REMARKS

Status of the claims

Claims 1-73 were originally presented for examination on October 24, 2001. In a Preliminary Amendment dated April 9, 2003, claims 8, 9 and 37-39 were cancelled and claims 1, 34, 40, 44, 65, 67, 72 and 73 were amended. As a result, claims 1-7, 10-36 and 40-73 were pending. In response to a Restriction Requirement dated September 15, 2004, claims 1-7, 10-14, 19-33, and 44-73 were withdrawn from consideration; following which claims 1-7, 10-36 and 40-73 were pending and claims 34-36 and 40-43 were under consideration. It is noted that the Office Action states that claims 1-7, 10-14, 19-36 and 40-73 are presently pending. Applicants believe this statement is in error, inasmuch as claims 15-18 are also pending. Clarification is requested.

To summarize, claims 1-7, 10-36 and 40-73 are presently pending, as shown above, and claims 34-36 and 40-43 are under consideration. Claim 40 has been amended as shown above. Support is found, for example, at page 33, lines 13-25. Applicants note that process claims 1-33 and 44-73 depend from, and contain all the limitations of product claim 40 and are therefore eligible for rejoinder upon allowance of claim 40.

Claim numbering

Applicants note the intention of the Office to renumber the claims prior to issuance. Office Action, page 2.

35 U.S.C. § 112, first paragraph

Claims 34-36 and 40-43 stand rejected as allegedly failing to comply with the written description requirement. Office Action, pp. 2-6. It is alleged that the genus of fusion molecules encompassed by the claims is unduly broad and that "the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus." Office Action, pages 5-6. The position of the Office appears to be that amino acid sequences of the histone modifying enzyme portion, and detailed chemical structure and/or sequence of the DNA-binding portion, of the claimed fusion molecules is required.

In response, Applicants note that the written description requirement is highly fact-dependent and there is a strong presumption that an adequate written description of the claimed invention is present at the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976). The written description requirement of section 112 has never required that claims be limited in scope to particular sequences.

Furthermore, there is nothing inherently unpatentable about claims directed to a broad genus. Rather, the test for adequate written description is whether the specification reasonably conveys possession of the invention in view of a thorough reading of the disclosure and the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. *See, e.g., In re Lukach,* 169 USPQ 795, 796 (CCPA 1971). *In re Lange,* 209 USPQ 288 (CCPA 1981).

In a recent explication of this long-standing principle,[1] the Federal Circuit made clear that an applicant need not describe the exact chemical composition of every claimed combination, adding that neither the Patent Act nor case law requires such detailed disclosure. *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227 (Fed. Cir. 2000).

Applicants address the written description of each portion of the claimed fusion molecules below.

Chromatin remodeling portion

It appears that the Office's position is that an exact nucleotide or amino acid sequence is required for every single claimed enzymatic chromatin remodeling component. This position is contrary to Statute and case law (*see, e.g., Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227, 1232-33 (Fed. Cir. 2000) (emphasis added)):

[1] and subsequent to its *University of California v. Eli Lilly and Co.* decision

> However, neither the Patent Act nor the case law of this court requires such detailed disclosure. [Referring to description of the exact chemical composition of claimed gasoline formulations] . . . issue is whether one skilled in the art could derive the claimed ranges from the [ ] disclosure [citing *In re Hayes Microcomputer Prods., Inc.*, 982 F.2d 1527, 1533, 25 USPQ2d 1241, 1245] . . . Rather, the Patent Act and this court's case law require only sufficient description to show one of skill in the [ ] art that the inventor possessed the claimed invention at the time of filing.
>
> The written description requirement does not require the applicant "to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." citing *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)

Applying this well-settled law to the claims at issue, it is clear that a molecular biologist skilled in the field of chromatin modification would have been aware, as of the filing date, that Applicants were in possession of fusion molecules comprising the recited chromatin remodeling portions. Indeed, the existence, structure and properties of histone methyltransferases, histone kinases and phosphatases, histone ubiquitinating and de-ubiquitinating enzymes and histone proteases are described in the specification as filed, for example, at page 33, lines 13-25 of the specification.

To provide but a single example of the knowledge of the skilled artisan, the reference cited at page 33, line 19 (Jenuwein *et al.* (2001) *Science* **293:**1074-1080)[2] describes the histone methyltransferases *Su(var)3-9*, *Clr4*, *SUV39H1* (page 1076, column 1), G9a (page 1076, column 3), CARM1 and PRMT1 (page 1077, column 2). It also describes ubiquitination of histone H1 by $TAF_{II}250$, the rph6 histone ubiquitinating protein, a histone de-ubiquitinating enzyme and a histone protease (all at page 1078, column 3). Additionally, Jenuwein *et al.* refers to the detailed characterization of histone phosphorylation and dephosphorylation systems (page 1076, column 1) citing Hsu *et al*

[2] Copy attached as Exhibit A

(2000) *Cell* **102:**279-291.[3] Hsu *et al.* describes histone kinases and phosphatases in yeast and nematodes.

One of skill in the art, if not already aware of the Jenuwein reference, would certainly have been directed to it by the specification. Thus, with respect to the proper criteria, the specification meets the written description requirement because it more than adequately conveys to one of skill in the art that Applicants were in possession of fusion molecules comprising the recited chromatin remodeling proteins.

The Office's assertion that an adequate written description requires a listing of explicit sequences is also untenable. Determining whether the written description requirement is satisfied is a question of fact. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *Regents of University of California v. Eli Lilly* 43 USPQ2d 1398 (Fed. Cir. 1997). The burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed subject matter at the time of filing. Indeed, there is a strong presumption that an adequate written description is present when the application is filed. (See, *e.g.,* Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099, citing *In re Wertheim*, 191 USPQ 90 (CCPA 1976)). The Guidelines state:

> The description need only describe in detail that which is new or not conventional. This is equally true whether the claimed invention is a product or a process. (Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099).

The Federal Circuit in *Union Oil* is in accord (*Union Oil,* 54 USPQ2d at 1233, 1235 and 1229):

> The inquiry for adequate written description simply does not depend on a particular claim format, but rather on whether the patent's description would show those of ordinary skill in the [ ] art that the inventors possessed the claimed invention at the time of filing.

[3] Copy attached as Exhibit B

> . . . as this court's predecessor explained . . .
> If lack of literal support alone were enough to support a rejection under § 112, then the statement of *In re Lukach* ... that "the invention claimed does not have to be described *in ipsis verbis* in order to satisfy the written description requirement of § 112," is empty verbiage.
>
> Thus the claims which define the invention in terms of various characteristics also inform those of skill in the art of the composition of the claimed gasoline fuels.

Simply put, applicants need only show that the original disclosure conveys to one of skill in the art that they were in possession of the claimed subject matter at the time of filing. *In re Wertheim,* 191 USPQ 90 (CCPA 1976). There is no requirement that each and every sequence falling within the scope of the claims be set forth in the specification as filed, when, as in the pending case, the specification clearly demonstrates possession of structures and function of the recited molecules. For this reason as well, the rejection should be withdrawn.

DNA-binding portion

With respect to the DNA-binding portion of the claimed fusion molecules, and in light of applicable law as summarized above, it is clear that one of skill in the art would be aware of the structures and properties of the DNA-binding domains disclosed, for example, at page 30, line 4 through page 32, line 21. For example, triplex-forming oligonucleotides have been described in U.S. Patent Nos. 5,422,251; 5,693,471; 5,789,155; 5,874, 555; and 5,928,863 (all issued before the August 28, 2000 priority date of the present application), as well as WO94/17092 and WO 96/40711. Additionally, U.S. Patents 6,403,302; 6,426,407; and 6,432,638 relating to triplex-forming oligonucleotides have now issued and all are reflective of the state of the art regarding triplex-forming oligonucleotides at the time the specification was filed. The existence of this extensive patent literature[5] attests to the fact that triplex-forming oligonucleotides

[5] as well as an extensive collection of non-patent literature not listed here, but some of which is cited in the patents listed above

and their DNA-binding properties were well-known to those of skill in the art at the priority date and, accordingly, that the skilled artisan would have known that Applicants were in possession of the claimed subject matter at the time of filing.

Minor groove binders and their DNA-binding properties have been described, for example, in U.S. Patents 5,998,140 and 6,090,947 (both of which issued before the priority date of the present application), as well as WO 96/32496 (as cited in the specification at page 30, lines 21-23). Additionally, U.S. Patents 6,143,901; 6,303,312; 6,472,537; and 6,506,906 relating to minor groove binders have now issued, and all are reflective of the state of the art regarding minor groove binders as of the priority date of the present application.

Zinc finger DNA-binding domains are described, for example, at page 25, lines 3-26 and at page 31, line 27 through page 32, line 5 and in the references cited in those passages, as would be available to one of skill in the art.

Thus, the specification clearly describes the structure and DNA-binding properties of the claimed DNA-binding domains, adequately conveying their possession to one of skill in the art.

Conclusion

It is axiomatic that there is no requirement for *in ipsis verbis* support for claimed subject matter. Rather, all that is required is that the specification reasonably convey possession of the invention. *See, e.g., In re Lukach,* 169 USPQ 795, 796 (CCPA 1971). As should be clear from the case law and remarks set forth above, Applicants have clearly communicated possession of the claimed subject matter to the skilled artisan. Accordingly, the written description requirement has been fulfilled, and the rejection should be withdrawn.

35 U.S.C. § 102(e)

Claims 34-35 and 40-43 stand rejected as allegedly anticipated by U.S. Patent No. 6,534,261 (Cox *et al.*). Office Action, pp. 6-7. The Office states that the '261 patent discloses a ZFP-KRAB fusion protein, that the KRAB domain interacts indirectly with

HP1 through KAP-1 and that HP1 is involved in histone methylation. Based on this chain of reasoning, it is alleged that the '261 patent's disclosure of a ZFP-KRAB fusion protein anticipates claimed fusion molecules comprising a zinc finger domain and a component of a chromatin remodeling complex having histone methylase activity.

Applicants traverse the rejection because the '261 patent fails to disclose each and every element of the claimed subject matter. Independent claim 40 recites a fusion molecule that comprises, *inter alia*, a histone methyltransferase or functional fragment thereof. The histone methyltransferase is further identified in claim 40 as an enzymatic component of a chromatin remodeling complex.

By contrast, the Office Action states that "[t]he KRAB domain interacts *indirectly* with HP1 through KAP-1 and an intrinsic property of HP1 is "*involvement in* histone methylation." (Office Action, page 7, emphasis added.) From this, the Office apparently concludes that HP1 is an enzymatic component of a chromatin remodeling complex.

However, neither the facts nor the Office's chain of reasoning lead to the conclusion that the '261 patent's disclosure of a ZFP-KRAB fusion anticipates, for the following reasons:

1. The cited reference does not teach, either explicitly or inherently, that HP1 is a histone methyltransferase

2. Even if HP1 were a histone methyltransferase, the '261 patent does not disclose a ZFP-HP1 fusion.

With respect to the first point, the '261 patent does not teach that the HP1 protein is a histone methyltransferase, and the Office has provided no evidence to that effect, stating merely that HP1 is "involved" in histone methylation. In fact, the Ayyanathan reference cited by the Office states that HP1 is retained in a repressor-corepressor complex by Lys9-methylated histone H3, but identifies the Lys9-specific histone methyltransferase as the SETDB1 protein (*see* Ayyanathan at page 1855, Abstract). Thus, even if the claims recited indirect interaction between a DNA-binding domain and a histone methyltransferase (which they do not), the '261 patent (in light of Ayyanathan) fails to disclose such interactions, either explicitly or inherently.

With respect to the second point, Applicants note that claim 40 recites a fusion of a DNA-binding domain with an enzymatic component of a chromatin remodeling complex or a functional fragment thereof, and further recites specific enzymatic components. Importantly, it does not recite a fusion of a DNA-binding domain with a protein that interacts with an enzymatic component of a chromatin remodeling complex. Thus, even if HP1 were a histone methyltransferase (which, as shown above, it is not), the '261 patent does not disclose a fusion between a DNA-binding domain and HP1.

In conclusion, inasmuch as the '261 patent discloses a ZFP-KRAB fusion and the Office agrees that KRAB is not an enzymatic component of a chromatin remodeling complex[6], the '261 patent fails to anticipate the claimed subject matter and the rejection should be withdrawn.

Double patenting

Claims 34-35 and 40-43 stand provisionally rejected, under the judicially-created doctrine of obviousness-type double patenting, over claims 34-37 and 40-42 of copending USSN 09/844,508 in view of the '261 patent (cited above under 35 U.S.C. § 102) as evidenced by Ayyanathan *et al.*

For the reasons advanced above relating to 35 U.S.C. § 102(e), Applicants maintain that the '261 patent fails to teach, explicitly or inherently, any of the claimed fusion molecules.

In addition, Applicants note that the reference application is the parent of the present application and was subject to a Restriction Requirement identifying ten groups of claims. (*See* USSN 09/844,508 Office Action dated November 19, 2002.) Applicants note further that the reference claims have been withdrawn from consideration (with no possibility of rejoinder) in the reference application. Specifically, reference claims 34-37 and 41 were placed in Group VII of the Restriction Requirement in the parent application (fusion polypeptide and cell comprising fusion polypeptide); while reference claims 40

[6] Indeed, the Examiner asserts, elsewhere in the Office action, that KRAB is not one of the claimed enzymatic components of a chromatin remodeling complex. *See* page 4 of Office Action, lines 3-5: "However, none of the foregoing defined structures [which includes KRAB] functions as a histone-methylase/demethylase, -kinase/phosphatase, -ubiquitinase, -ADP ribosylase or -protease."

(fusion polypeptide and cell comprising fusion polypeptide); while reference claims 40 and 42 were placed in Group IX (nucleic acid encoding fusion polypeptide and cell comprising the nucleic acid). By way of comparison, presently pending claims 34, 35, 40 and 42 correspond to Group VII of that Restriction Requirement (fusion polypeptide and cell comprising fusion polypeptide); while presently pending claims 41 and 43 correspond to Group IX of that Restriction Requirement (nucleic acid encoding fusion polypeptide and cell comprising the nucleic acid). In other words, the Office has already determined that the claims presently under consideration are patentably distinct from the reference claims. In view of this fact, and inasmuch as there is no possibility of rejoinder of Groups VII and IX with elected Group I in reference application USSN 09/844,508, Applicants believe this provisional rejection is in error and should be withdrawn. At the very least, Applicants request that this provisional rejection be held in abeyance until the issuance of either the present application or the reference application.

CONCLUSION

Applicants believe that the claims under consideration are allowable, and look forward to notification that process claims 1-33 and 44-73 have been rejoined. Inasmuch as those process claims contain all the limitations of the composition claims, Applicants believe they are allowable as well.

Respectfully submitted,

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